



FULL TEXT OF CASES (USPQ FIRST SERIES)In re Merck & Co., Inc., 231 USPQ 375 (CA FC 1986)

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In re Merck & Co., Inc.**(CA FC)****231 USPQ 375****Decided September 8, 1986****No. 85-2740****U.S. Court of Appeals Federal Circuit****Headnotes****PATENTS****1. Patentability -- Invention -- Specific cases -- Chemical -- (§ 51.5093)**

Board of Patent Appeals and Interferences' decision sustaining rejection for obviousness of reexamination claims for antidepressant drug amitriptyline was proper, since claimed drug is structurally similar to other prior art psychotropic compound, imipramine, which is known to possess antidepressive properties, and thus one skilled in medicinal chemical arts would have expected amitriptyline to resemble imipramine in alleviation of depression in humans.

Case History and Disposition:

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Appeal from Patent and Trademark Office Board of Patent Appeals and Interferences.

Reexamination request, Control No. 90/000264, to reexamine patent of Edward L. Englehardt, Patent No. 3,428,735, issued February 18, 1969, on application, Serial No. 662,907, filed August 24, 1967, as continuation-in-part of application Serial No. 855,981, filed November 30, 1959. From decision sustaining decision rejecting claims 1-3 in reexamination application, applicant appeals. Affirmed; Baldwin, Circuit Judge, dissenting with opinion.

Attorneys:

Charles M. Caruso, Rahway, N.J. (Nels T. Lippert, and Fitzpatrick, Cella, Harper & Scinto, New York, N.Y., on the brief, and Mario A. Monaco, and Michael C. Sudol, Jr., both of Rahway, N.J., of counsel) for appellant.

Richard E. Schafer, Associate Solicitor (Joseph F. Nakamura, Solicitor, and Fred E. McKelvey, Deputy Solicitor, on the brief) for Patent and Trademark Office.

Donald R. Dunner, and Finnegan, Henderson, Farabow, Garrett & Dunner, both of Washington, D.C. (Robert D. Bajefsky, Carol P. Einaudi, and Finnegan, Henderson, Farabow, Garrett & Dunner, all of Washington, D.C., on the brief, and Beryl L. Snyder, Elmwood Park, N.J., of counsel) for intervenor Biocraft Laboratories, Inc.

Judge:

Before Davis, Baldwin, and Archer, Circuit Judges.

Opinion Text

Opinion By:

Davis, Circuit Judge.

This is an appeal from a final decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), sustaining the rejection of claims 1 through 3 in the reexamination application ¹of U.S. Patent No. 3,428,735 ²(the '735 patent) as unpatentable under 35 U.S.C. § 103. We affirm.

I. BACKGROUND

A. The Invention

The invention is directed to a method of treating human mental disorders; the method involves treating depression in humans by the oral administration of 5-(3-dimethylaminopropylidene) dibenzo [a,d] [1,4] cycloheptadiene (commonly known as and hereafter referred to as "amitriptyline"), or the hydrochloride or hydrobromide salts thereof,

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in a particular dosage range. Amitriptyline has the following chemical structure:

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As representative of the invention, claim 1 reads:

1. A method of treating human mental disorders involving depression which comprises orally administering to a human affected by depression 5-(3-dimethylaminopropylidene) dibenzo [a,d] [1,4] cycloheptadiene or its non-toxic salts in daily dosage of 25 to 250 mg. of said compound.

Remaining claims 2 and 3 are dependent from claim 1 and add limitations pertaining to the use of the hydrochloride and hydrobromide salts of amitriptyline, respectively.

B. Related Proceedings

On March 10, 1977 an application, Serial No. 776,464 (the '464 application), was filed for reissue of the '735 patent. ³All the claims of the '464 application were finally rejected by the examiner under section 102 of title 35, United States Code, and alternatively under section 103 of that title.

Subsequently, an appeal (Appeal No. 424-40) was taken to the Board ⁴which affirmed the examiner's rejections. Additionally, the Board entered a new rejection under 35 U.S.C. § 103 over a combination of references not previously cited by the examiner. In accordance with 37 C.F.R. § 1.196(b) (1985) ⁵, appellant elected reconsideration of the '464 application by the examiner. The examiner maintained the rejection entered by the Board; in Appeal No. 480-01, the Board affirmed the examiner. The Board's decision was appealed to the Court of Customs and Patent Appeals (CCPA). Upon the motion of the Commissioner of Patents and Trademarks and on the authority of

In re Dien, 680 F.2d 151, 214 USPQ 10 (CCPA 1982), the appeal was dismissed for lack of subject matter jurisdiction. ⁶

The reissue application was protested by Biocraft Laboratories, Inc. (Biocraft), intervenor in the current appeal. Biocraft is also the plaintiff in a related litigation pending in the U.S. District Court for the District of New Jersey in which the validity and infringement of the '735 patent is in issue. *See Biocraft Laboratories Inc. v. Merck & Co.*, Civil Action No. 77-0693 (D.N.J.). The district court has stayed further action in that case pending the final outcome of the pending PTO proceedings.

C. Reexamination Proceeding

Following dismissal of the reissue appeal by the CCPA, Merck & Co., Inc. (Merck), the assignee of the '735 patent, filed for and was granted a request for reexamination of the patent. As a result of prosecution before the examiner, claims 1 through 3 of the reexamination application were finally rejected under 35 U.S.C. § 102 as anticipated by prior art references; the claims were also rejected under 35 U.S.C. § 103 as being obvious over references cited by the Board in its new ground of rejection entered during the initial reissue appeal. Finding the '735 patent to be entitled to the benefit of the November 30, 1959 filing date of its parent application, Serial No. 855,981, the Board reversed the section 102 rejection because the effective filing date of the application antedated all the references cited therein. The Board, however, sustained the rejection for obviousness under section 103. Expressly adopting the reasonings of its earlier reissue opinions, the Board took the position that in view of the prior art, in combination, and a thorough knowledge of the investigative techniques used in the medicinal chemical art, the skilled artisan would have expected the known tricyclic compound, amitriptyline, to be useful as an antidepressant.

D. The References

The references relied upon by the Board were:

(1) Rey-Bellet et al (Rey-Bellet) U.S. Patent No. 3,384,663, May 21, 1968 (application filed Mar. 27, 1959);

(2) Kuhn, *Schweizerische Medizinische Wochenschrift*, Vol. 87, No. 35-36, pp. 1135-1140 (Aug. 1957)

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(3) Lehman et al. (Lehman), *Canadian Psychiatric Association Journal*, "The Treatment of Depressive Conditions with Imipramine (G 22355)", vol. 3, No. 4, pp. 155-164 (Oct. 1958);

(4) Friedman, *First Symposium On Chemical Biological Correlation*, "Influence of Isosteric Replacements Upon Biological Activity", pp. 296-358 (May 1950);

(5) Burger, *Journal of Chemical Education*, "Rational Approaches to Drug Structure", Vol. 33, No. 8, pp. 362-372 (Aug. 1956);

(6) Petersen et al. (Petersen), *Arzneimittel-Forschung*, Vol. 8, No. 7, pp. 395-397 (1958);

(7) Roche Research Report No. 43,162, pp. 1-9 (Nov. 1957);

(8) Roche Research Report No. 43,169, pp. 1-8 (Apr. 1958);

(9) Roche Research Report No. 52,195, pp. 1-13 (Sept. 1958) (Collectively called the "Roche Reports").

The Rey-Bellet patent disclosed amitriptyline and its hydrochloride salt. Properties of amitriptyline

taught by the reference included a "manifold activity upon the central nervous system," as well as pharmacological and medicinal properties, such as "narcosis-potentiating, adrenolytic, sedative, antihistaminic, antiemetic, antipyretic and hypothermic." Rey-Bellet did not disclose or otherwise teach that amitriptyline possessed antidepressive properties.

The Kuhn publication disclosed the compound, imipramine, and taught that the compound was a very effective antidepressant in humans. Imipramine has the chemical structure
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and differs from the structure of amitriptyline only in the replacement of the unsaturated carbon atom in the center ring with a nitrogen atom. Kuhn taught a recommended dosage of 75-150 mg per day -- possibly 200-250 mg if the smaller doses proved ineffective.

The Lehman publication disclosed the results of a Canadian study of the effects of imipramine on the symptoms of depression in humans. This article confirmed, for the most part, the teachings of the Kuhn article.

The object of the Friedman publication was "to survey the history of isosterism, to classify the varieties of isosteric replacements which are recorded in the literature, and to note the influence of these replacements on the biological activity of compounds." Friedman defined isosteres as atoms, ions or molecules in which the peripheral layers of electrons can be considered identical. Compounds which fit this broad definition and exhibit the same biological activity were termed "bioisosteric." Further, with respect to the medicinal chemists' use of the theory of "isosteric replacement" or "bio-isosteric replacement" as a tool to predict the properties of compounds, Friedman commented that:

[t]o the synthetic organic chemist interested in medicinal chemistry, every physiologically active compound of known structure is a challenge - a challenge either to better it, or perhaps merely to equal it. . . .

There are numerous ways of attacking such a problem. . . . One of the methods which has been used frequently, very often with success, is that of isosteric replacement. The examples of this type of replacement in the literature are very numerous, and the fruitful results in the fields of sulfonamides, antimetabolites, and antihistamines are well known.

Friedman at page 296. Finally, Friedman disclosed various atoms or groups of atoms as bioisosteric, including the interchange of oxygen and the unsaturated carbon atom which often resulted in similar biological activity. Friedman, however, did not disclose or otherwise teach as bioisosteric the interchange of the nitrogen and unsaturated carbon atoms.

The Burger publication also discussed the theory of "bioisosterism" and its usefulness in designing new drugs based upon the knowledge of "lead" compounds.

The Petersen publication taught, *inter alia*, the properties of chlorpromazine (a phenothiazine derivative) and chlorprothixene (a 9-amino-alkylene-thioxanthene derivative), these compounds have the following structural formulas:

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Petersen concluded that, when the nitrogen atom located in the central ring of the phenothiazine compound is interchanged with an unsaturated carbon atom as in the corresponding 9-aminoalkylene-thioxanthene compound, the pharmacological properties of the thioxanthene derivatives resemble very strongly the properties of the corresponding phenothiazines. Using the theory of isosteric replacement, Petersen predicted this similarity in properties:

Structural chemical considerations permitted the expectation that the 9-aminoalkylene-thioxanthenes . . . would show great similarity to the corresponding phenothiazines. They should be more similar in their behavior to that of the phenothiazines than the saturated 9-aminoalkyl-thioxanthenes. From the physical point of view the p- electron distributions (sites of p - electrons) are almost the same in the phenothiazine derivatives and in the 9-aminoalkylene-thioxanthenes with their stabilizing conjugated double linkage between C9 in the thioxanthene ring and the first C-atom of the side chain.

Petersen at page 3. The compounds were disclosed as having a strong central depressive, i.e., tranquillizing, action in animals.

The Roche Reports revealed the results from tests comparing the pharmacological properties of amitriptyline and imipramine. The reports indicated that the two compounds were very similar in a variety of properties, including their action as tranquilizers having narcosis-potentiating effects. Because of this similarity and because amitriptyline and imipramine were structurally related, Roche scientists concluded that amitriptyline should be clinically tested for depression alleviation -- a known property of imipramine. In the pharmacological guideline for the clinical testings of amitriptyline (which was labelled Roche Preparation Ro 4-1575), the Roche Reports stated that

[i]t is to be noted that a "tofranil-like effect" is already to be expected by using a dose $\frac{1}{4}$ -- $\frac{1}{2}$ that of Tofranil. Side effects which can appear . . . are sedative and atropine-like effects, such as appear also with Tofranil. ²

We must decide in this appeal whether appellant's invention would have been prima facie obvious over the available prior art of record; and, if so obvious, whether the prima facie case has been rebutted by evidence of unexpected results.

III. DISCUSSION

In its opinion on this problem, the Board expressly followed the guidelines of *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 466-67 (1966), and made findings on factual inquiries specifically set forth in that decision. These factual findings must be accepted unless they are clearly erroneous. *In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984), *cert. denied*, 105 S.Ct. 1173 (1985); *In re De Blauwe*, 736 F.2d 699, 703, 222 USPQ 191, 193 (Fed. Cir. 1984); *accord Stock Pot Restaurant, Inc. v. Stockpot, Inc.*, 737 F.2d 1576, 1578-79, 222 USPQ 665, 666-67 (Fed. Cir. 1984). In this case we do not hold the Board's factual findings -- as to the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the art -- to be clearly erroneous and accordingly we have followed them in our statement of the prior art and we now follow them in our analysis of the legal issue of obviousness.

Prima Facie Obviousness: The prior art taught that amitriptyline and imipramine are both psychotropic drugs which react on the central nervous system and which were known in the art prior to the time of appellant's invention. Imipramine was known to possess antidepressive properties in humans. While amitriptyline was known to possess psychotropic properties such as sedative and narcosis-potentiating properties, the drug was not known to be an antidepressant. However, the prior art has shown that imipramine and amitriptyline are unquestionably closely related in structure. Both compounds are tricyclic dibenzo compounds and differ structurally only in that the nitrogen atom located in the central ring of imipramine is interchanged with an unsaturated carbon atom in the central ring of amitriptyline. To show obviousness, it was necessary to determine from knowledge

already available in the art at the time of appellant's invention that one skilled in the medicinal chemical art would have expected amitriptyline, like imipramine, to be useful in the treatment of depression in humans. *In re*

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Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

As found by the Board, the Roche Reports recognized the structural relationship between amitriptyline and imipramine and concluded that amitriptyline should be tested for its anti-depressant activities. In fact the Roche Reports expressly stated that amitriptyline was expected to resemble imipramine clinically in its depression alleviation effects.

"Structural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). However, the Board did not rest its conclusion of obviousness on structural similarity alone. Rather, the Board further recognized that in attempting to predict the biological activities of a drug, a skilled medicinal chemist would not proceed randomly, but would base his attempts on the available knowledge of prior research techniques, and literature used in his field. The prior art showed that one such technique was "bioisosteric replacement" or the theory of bioisosterism -- where the substitution of one atom or group of atoms for another atom or group of atoms having similar size, shape and electron density provides molecules having the same type of biological activity. Finding that the Friedman, Burger and Petersen references taught that bioisosterism was commonly used by medicinal chemists prior to 1959 in an effort to design and predict drug activity, the Board concluded that one of ordinary skill in the arts would have been aware of this technique at the time of appellant's invention. ⁸Further, the Board found that Petersen taught as bioisosteric the interchange of the nitrogen and unsaturated carbon atoms -- the precise structural difference between imipramine and amitriptyline. ²

We see no clear error in the Board's determination as to the teachings of the prior art references, in combination. In view of these teachings, which show a close structural similarity and a similar use (psychotropic drugs) between amitriptyline and imipramine, one of ordinary skill in the medicinal chemical arts, possessed of the knowledge of the investigative techniques used in the field of drug design and pharmacological predictability, would have expected amitriptyline to resemble imipramine in the alleviation of depression in humans. Accordingly, we agree with the Board that appellant's invention was prima facie obvious over the prior art of record.

In traversing the Board's decision of obviousness, appellant has urged that the Board's decision was premised on an impermissible "obvious to try" standard. Appellant contends that there was no motivation in the prior art to arrive at appellant's invention. "[O]bvious to try is not the standard of 35 U.S.C. § 103." *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977) (emphasis omitted). Rather, the test is whether the references, taken as a whole, would have suggested appellant's invention to one of ordinary skill in the medicinal chemical arts at the time the invention was made. *In re Simon*, 461 F.2d 1387, 1390, 174 USPQ 114, 116 (CCPA 1972). Clearly, amitriptyline and imipramine, both known psychotropic drugs, are closely structurally related. The expectation that the similar structures would behave similarly was suggested in the Roche Reports. In combination with those teachings, the prior art teaching that the precise structural difference between amitriptyline and imipramine involves a known bioisosteric replacement provides sufficient basis for the required expectation of success, without resort to hindsight. ¹⁰Obviousness does not require absolute predictability. *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976). Only a reasonable expectation that the beneficial result will be achieved is necessary to show obviousness. *In re Longi*,

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759 F.2d 887, 897, 225 USPQ 645, 651 (Fed. Cir. 1985).

We also find untenable appellant's arguments that Petersen teaches away from appellant's invention. Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Thus, Petersen must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole. That teaching is that the interchange of the nitrogen and the unsaturated carbon atoms is isosteric and compounds so modified are expected to possess similar biological properties.

Neither are we persuaded by appellant's contention that the Board erred in relying on the contemporaneous independent invention of others to support its holding of obviousness.¹¹ As we have said earlier, the teachings of the prior art references in combination adequately support the Board's conclusion. However, the additional, although unnecessary, evidence of contemporaneous invention is probative of "the level of knowledge in the art at the time the invention was made." *In re Farrenkopf*, 713 F.2d 714, 720, 219 USPQ 1, 6 (Fed. Cir. 1983).

Unexpected Results: A prima facie case of obviousness can be rebutted by evidence of unexpected results. *In re Davis*, 475 F.2d 667, 670, 177 USPQ 381, 384 (CCPA 1973). In rebuttal of the PTO's prima facie case appellant has asserted that, as compared to imipramine, amitriptyline unexpectedly has a more potent sedative and a stronger anticholinergic effect. In support of this contention, appellant has relied on an affidavit of Dr. Joseph J. Schildkraut,¹² a psychiatrist and a Professor of Psychiatry at Harvard, and also on a published record of a symposium of physicians and psychiatrists concerned with the treatment of the depressed patient.¹³

Dr. Schildkraut's affidavit recognizes some pharmacological differences between amitriptyline and imipramine including the fact that amitriptyline is a more potent sedative and has a strong anticholinergic effect than imipramine. Further, Dr. Schildkraut notes that depressed patients have responded differently to amitriptyline and imipramine, some responding to one and not the other or more favorably to one than to the other. For the most part, the record of the cited symposium confirms the differences noted in the Schildkraut affidavit.¹⁴ That record also counseled practicing physicians on choosing from the spectrum of tricyclic antidepressants (a term which includes amitriptyline and imipramine) the particular drug useful for an individual patient.

After a careful consideration of all the evidence, we are persuaded that the Board did not err in determining that the alleged unexpected properties of amitriptyline are not so unexpectedly different from the properties of imipramine, the closest prior art, as to overcome the prima facie showing of obviousness. The prior art of record clearly taught that amitriptyline was a known sedative.¹⁵ The evidence before us (which was, of course, before the Board) further revealed that all tricyclic antidepressant drugs, in general, possess the secondary properties of sedative and anticholinergic effects. Specifically, the record showed that during the prosecution of the reissue application, appellant submitted an article entitled "Using the tricyclic antidepressants" which included a table comparing the properties of known tricyclic antidepressant drugs.¹⁶ Included in these properties were sedative and anticholinergic effects of the known antidepressants.¹⁷ Thus, it appears that the alleged difference in properties between amitriptyline and imipramine is a matter of degree rather than kind. Moreover, as to the sedative effects, the article revealed only a slight difference between the two compounds. Amitriptyline was characterized as "highly sedative" while imipramine was only "somewhat less [sedative] than amitriptyline."¹⁸ Regarding

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the anticholinergic effect, the article showed that both drugs have anticholinergic effects but to a different degree. These are not truly unexpected results. The Board found in one of its reissue opinions (incorporated in the reexamination decision now on appeal): "[i]n regard to the sedative and anticholinergic properties of amitriptyline, we are not convinced that the side effects of this material [amitriptyline] are significantly or unexpectedly different from the level of those properties exerted

by the closest prior art antidepressant, imipramine.¹⁹

The core of it is that, while there are some differences in degree between the properties of amitriptyline and imipramine, the compounds expectedly have the same type of biological activity. In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the prima facie case. The fact that amitriptyline and imipramine, respectively, helped some patients and not others does not appear significant. As noted by the Board, a difference in structure, although slight, would have been expected to produce some difference in activity.

[1] In sum, we hold that the claimed invention would have been obvious to one of ordinary skill in the art. Accordingly, the decision of the Board is

AFFIRMED.

Footnotes

Footnote 1. *Ex Parte Merck and Co.*, Reexamination No. 90/000264, Appeal No. 607-66 (PTO Bd. Pat. App. & Int., May 28, 1985), JA p.7. In its opinion the Board expressly adopted the reasonings in its earlier reissue (for the '735 patent) opinions, *Ex Parte Edward L. Engelhardt*, Reissue Application No. 776,464, Appeal No. 424-40 (PTO Bd. Pat. App., Apr. 23, 1980), JA p. 13 and *Ex Parte Edward L. Engelhardt*, Reissue Application No. 776, 464, Appeal No. 480-01 (PTO Bd. Pat. App., Fed. 25, 1982), JA p. 23.

Footnote 2. U.S. Patent No. 3,428,735, issued to Edward L. Engelhardt on February 18, 1969, was based on patent application Serial No. 662,907 filed August 24, 1967 as a continuation-in-part of patent application Serial No. 855,981 filed Nov. 30, 1959.

Footnote 3. The reissue application was filed as a "no defect" type reissue under the then existing 37 C.F.R. § 1.175(a)(4) (1980). That provision has now been repealed.

Footnote 4. At that time, the Board of Patent Appeals and Interferences was called the Board of Patent

Footnote 5. 37 C.F.R. § 1.196(b) provides that when the Board of Appeals determines a new ground of rejection, the appellant may

- (1) after submitting appropriate amendments or showing of facts, have the matter reconsidered by the examiner;
- (2) waive reconsideration before the examiner and have the case reconsidered by the Board;
or
- (3) treat the decision, including the new ground of rejection, as a final decision in the case.

Footnote 6. *See In the Matter of the Application of Edward L. Engelhardt*, Appeal No. 82-611 (CAFC Oct. 28, 1982) (order granting motion to dismiss).

Footnote 7. Tofranil is a tradename used for imipramine.

Footnote 8. Appellant submitted the declaration of Dr. Paul N. Craig, an experienced medicinal chemist, JA p. 372. His view was that the concept of bioisosterism could not be used in 1959 to predict the antidepressant effects in amitriptyline or the pharmacological differences between imipramine and amitriptyline. Dr. Craig stated:

[I]n my opinion "isosterism" in 1959 afforded no basis for predicting the specific pharmaceutical utility in humans, and it is my belief that that is still true today I do not believe the carryover of tranquilizing activity from chlorpromazine to chlorprothixene afforded a reasonable basis for predicting the carryover of antidepressant properties from imipramine to amitriptyline.

Affidavit of Paul N. Craig, JA, pp. 374-75.

Plainly the Board was not clearly erroneous in discounting that testimony. There was independent evidence in the record to the contrary. The Friedman, Burger and Petersen references recognize that concept as a means of predicting biological properties in isosterically-related compounds prior to 1959.

Footnote 9. Petersen even went so far as to suggest that the apparent bioisosteric relationship between the interchange of the nitrogen and unsaturated carbon atoms led to the design of chlorprothixene in the expectation that the compound would share the same biological activity as chlorpromazine. *See Petersen, supra*, at p. 395.

Footnote 10. The teachings of the Roche Reports as well as the Petersen reference distinguish this case from *In re Grabiak*, 769 F.2d 729, 731, 226 USPQ 870, 871 (Fed. Cir. 1985) ("there is no motive in the cited art to make the modification required to arrive at appellants' compounds").

Footnote 11. *Ex Parte Edward L. Engelhardt*, Appeal No. 424-40, *supra* note 1, at pp. 23-24, JA pp. 22(l)-22(m), where the Board indicated that evidence before it revealed that four other groups of inventors independently and contemporaneously discovered amitriptyline's antidepressant properties using reasoning based on a thorough knowledge of investigative techniques, which included the concept of isosterism, used in the medicinal art area.

Footnote 12. Affidavit of Joseph J. Schildkraut, JA p.

Footnote 13. Symposium, *Depression Today -- Experts Answer Your Questions*, JA p.

Footnote 14. Dr. Schildkraut was a member of the

Footnote 15. Rey-Bellet, *supra*, col. 2, line 16.

Footnote 16. *Patient Care*, "Using the Tricyclic Antidepressants," pp. 28-33, 39-40, 43-45, 49-52, 57-58, 63-64, 67-68, 71, 75-76, 78, 81 84-85, (May 15, 1979); *see also* Commission's Appendix, pp. CA 17-45.

Footnote 17. *See also* the